REMARKS

The Enablement Rejection Under 35 USC § 112, first paragraph

The Office Action alleges without supporting evidence that all the claims are not enabled. The Examiner proposes that applicants come up with "a declaration utilizing the claimed compounds via the claimed pathway showing positive cancer treatment."

The unsuported rejection and the burden placed on applicants by the type of showing required are contrary to patent law.

First and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 209 USPQ 48 (1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.*

The Examiner has not established any basis to doubt objective enablement. The Examiner has also provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The rejection therefore is improper under *In re Marzocchi.*

The claims rejected are directed to compounds and to method claims for the treatment of cancerous cell growth, including in dependent claims, cell growth mediated by raf kinase, lung carcinoma, pancreas carcinoma, thyroid carcinoma, bladder carcinoma, colon carcinoma and myeloid leukemia, the treatment of which are not objectively doubtable. There is no indication that one of ordinary skill in the art would have questioned the effect of the drugs in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 04-1191, 04-1192 (Fed. Cir. June 27, 2005). This is especially true since, as admitted by the Office Action, compounds with the claimed activities are known, the ras/raf pathway is correlated with "many cancers," and that "arguably ... one of ordinary skill in the art in view of what is known in the art

would know how to practice the claimed invention." All the pieces of a proper enabling disclosure are admitted by the Office Action to have been met.

Additionally, pasted in next are two prior art abstracts regarding the state of the art linking raf kinase and cancer.

Antitumor activity of a phosphorothioate antisense oligodeoxynucleotide targeted against C-raf kinase. Monia, Brett P.; Johnston, Joseph F.; Geiger, Thomas; Muller, Marcel; Fabbro, Doriano. Department of Molecular Pharmacology, Isis Pharmaceuticals, Carlsbad, CA, USA. Nature Medicine (New York) (1996), 2(6), 668-675. Substantial evidence exists supporting a direct role for raf kinases in the development and maintenance of certain human malignancies. Here we test the potential of phosphorothioate antisense oligodeoxynucleotides targeted against human C-raf-1 kinase to specifically inhibit C-raf-1 kinase gene expression and tumor progression in cell culture and in vivo, using human tumor xenograft mouse models. Treatment of human tumor cells with appropriate phosphorothioate antisense oligodeoxynucleotides led to specific inhibition of C-raf kinase gene expression in cell culture and in vivo at well-tolerated doses. Moreover, oligodeoxynucleotide treatment resulted in potent antiproliferative effects in cell culture and potent antitumor effects in vivo against a variety of tumor types that were highly consistent with an antisense mechanism of action for these compds. These strongly suggest that antisense inhibitors targeted against C-raf-1 kinase may be of considerable value as antineoplastic agents that display activity against a wide spectrum of tumor types at well-tolerated doses. (Emphasis added.)

Raf-1 protein kinase is an integral component of the oncogenic signal cascade shared by epidermal growth factor and platelet-derived growth factor. Kizaka-Kondoh, Shinae; Sato, Ko; Tamura, Kazuyoshi; Nojima, Hiroshi; Okayama, Hiroto. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Molecular and Cellular Biology (1992), 12(11), 5078-86. Recent studies with cell mutants indicate that a cascade shared by the EGF and platelet-derived growth factor (PDGF) signals exist in NRK cells and mediates oncogenic signals induced by many oncogenes. The authors have employed the antisense RNA technique to investigate possible involvement of Raf-1 kinase in this signal transduction cascade. NRK cell clones highly reduced in the Raf-1 prodn. are generated by the expression of a c-raf-1 antisense RNA. They have no apparent growth defects and retain proper mitotic responses to growth factors but are refractory to transformation by EGF or PDGF plus transforming growth factor b, verbB, v-fms, v-K-ras, v-mos, v-fos, v-src, simian virus 40 large T, and polyomavirus middle T but not by v-raf or adenovirus E1A. These results not only support the authors' model for the oncogenic signal cascade but also lead to the conclusion that Raf-1 protein kinase is a downstream component of this oncogenic signal cascade shared by EGF and PDGF. (Emphasis added.)

As discussed above, this is adequate to objectively enable an invention. Without proper reason or evidence to doubt the objective truth of the enabling disclosure, the Examiner improperly requires a showing necessary for FDA approval, to support enablement. "Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal

evidence sufficient to convince such a person of the invention's asserted utility." *See In re Bundy*, supra. Thus, no showing is required in this case.

With respect to the type of showing required, under patent law, the requirement for examples of treatment in a patent application is contrary to law. As a matter of fact, there is no requirement for any examples in patent applications. See, for example, *In re Marzocchi*, 169 U.S.P.Q. 367 (1971), stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." (Emphasis added.) The MPEP in agreement with this by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." (Emphasis added.) See MPEP § 2164.02. No showing of "positive treatment," or, as a matter of fact, not even assurances of certain amounts of final use success, are required for an invention to be patentable, especially not in the pharmaceutical arts.

The Federal Circuit in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stated that with respect to the utility requirement

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott*, 34 F.3d 1058, 1063, 32 USPQ2d 115,1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

As stated in *In re Anthony*, 414 F2d 1383, 162 USPQ 594, 604 (CCPA 1969),

> Approval by the FDA, is not a prerequisite for the patenting of a new drug. . . . Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market, under the conditions prescribed, recommend or suggested in the proposed labeling thereof.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure only established the basic pharmacology for the compounds, but where no examples were provided. The specification stated that the compounds of the invention

possess activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity." Applicants disclose the activity of the claimed compounds and the Office Action even admits that one of ordinary skill in the art in view of what is known in the art would know how to practice the claimed invention. See page 3 of the Office Action.

Additionally, applicants respectfully disagree with the allegation that applicants have not demonstrated that the claimed compounds are active via the ras/raf pathway. The specification on pages 111-112 describe an in vitro raf kinase assay and indicate that all exemplified compounds from the specification (there are 397 of them), displayed IC_{50} values of between 1 nanomolar and 10 micromolar. No evidence has been presented which even suggests this data is not adequate to satisfy the requirements for enablement.

The quantity of any experimentation which may be necessary would not be undue. The specification teaches, for example, as discussed in the preceding paragraph, several specific ways in detail to test the compounds of the invention. Furthermore, applicants, for example, point to other known methods for the same. See, for example, page 113, lines 15-17. All one of ordinary skill in the art has to do is follow the direction of the specification to test the compounds of the invention. Dosages and methods of administration were also taught which can be perfected by running clinical trials, which are routine. The statute does not require that clinical trials be run to demonstrate methods of treatment claimed are enabled.

As discussed in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicants provide specific guidance as to how the claimed compounds can be tested for activity levels as discussed above in addition to showing that 397 species of the compounds claimed posses raf activity. Methods of administration of these compounds are also taught. Additionally, the state of the art, as is also admitted by the Office Action, is such that one of ordinary skill in the art would know how to proceed to test the efficacy of these compounds further if necessary.

However, that is no basis for an enablement rejection. The Office Action admits that raf/ras pathway is correlated to many cancers, some highly, some intermediately, and no

evidence has been presented which shows any of the compounds are inoperative. Even if the claims here are found to include inoperative embodiments, they would still meet the requirements of 35 U.S.C. §112. See *In re Sarett*, 140 USPQ 474 (CCPA 1964), stating that

> The function of claims is to *point out* the invention and *define* the scope of the monopoly, not to exclude substances which are possibly of no use in practicing the invention. (Emphasis added.)

and *In re Dinh-Nguyen*, 181 USPQ 46 (CCPA 1974), stating that

> It is *not a function of the claims* to specifically exclude either possible inoperative substances or ineffective reactant proportions. (Emphasis added.)

In the present case, if any inoperative embodiments were found, they would not diminish the numerous studies on the raf/ras pathway and related cancers thereto and the ability of one of ordinary skill in the art to practice the invention cases.

Applicants submit that all the claims are enabled, and that one of ordinary skill in the art in view of what is known in the art, can, without under experimentation, practice the claimed invention.

If the rejections are maintained, applicants request a specific explanation for the rejections of some of the more specific, i.e., narrower, dependent claims.

For example, claims 11, 15 and 41, are each directed to the use of a limited number of specifically named compounds. One of ordinary skill in the art, even assuming would need to test each of these compounds in a large number and type of cancer assays for activity, would have to perform only a limited number of tests, which is especially clearly not undue experimentation in this field.

Applicants also request that the rejection of narrower method claims, i.e., method claims 82-87, be explained as each names a specific cancer only. As the Office Action admits, ras/raf is already known to be effective in treating various cancers.

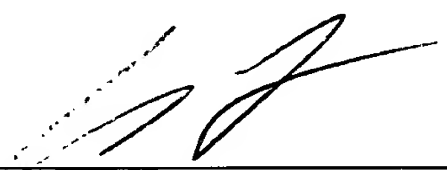
For all the foregoing reasons, reconsideration is respectfully requested.

The Written Description Rejection Under 35 USC § 112, first paragraph

The specification is amended to clarify what was intended.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Csaba Henter, Reg. No. 50,908
Richard J. Traverso, Reg. No. 30,595
Attorneys for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
Direct Dial: 703-812-5331
Facsimile: 703-243-6410

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